REMARKS

In the specification, the paragraphs beginning on page 21 at line 33 to page 22 at line 32 have been amended to provide updated references to the status of cited patent applications.

Claims 44-52, 54-57, 59-62, and 65-69 remain in this application. Claims 1-43, 53, 58, 63, and 64 have been cancelled. Claims 70-87 have been withdrawn.

Claims 44, 56, 57, 65, 67, and 69 have been amended. Support for amendment of Claim 44 is found throughout the specification, in particular on page 77 at line 31 line to page 78 at line 10. Claims 56 and 57 have been amended to delete the phrase "size-fractionated." Claim 65 has been amended to delete the term "about." Support for amendment of Claim 67 is found throughout the specification, in particular on page 37 at lines 21-25 and on page 38 at lines 8-16. Support for amendment of Claim 69 is found throughout the specification, in particular on page 77 at line 31 line to page 78 at line 10.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 44-68 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants point out that claim amendments discussed below have obviated these rejections and therefore, these rejections should be withdrawn.

In Claim 44, the term "the size-fractioned non-immunogenic soluble carrier" in step (b) allegedly lacks antecedent basis. (Office Action, page 2, lines 10-12) Claim 44 has been amended to delete the term "size-fractionated" and recite "the non-immunogenic soluble carrier subjected to the preparative sizing technique of step (a)." Amendment of Claim 44 has obviated this rejection of Claims 44-68 and therefore the rejection should be withdrawn.

Claims 44-69 stand rejected for allegedly omitting essential elements. (Office Action, page 2, lines 13-18). Claims 44 and 69 have been amended to recite a step of further fractionation. Claim 44 has been amended to recite "subjecting the conjugate preparation to size fractionation." Claim 69 has been amended to recite "subjecting the epitope-coupled construct to size fractionation, thereby yielding a non-immunogenic epitope-coupled construct which is free of high molecular weight immunostimulatory molecules." Amendment of Claims 44 and 69 have obviated this rejection of Claims 44-69 and therefore the rejection should be withdrawn.

Claim rejections under 35 U.S.C. § 112, first paragraph, written description

Claims 44-69 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. In particular, Claims 44 and 69 are rejected for allegedly containing new matter on grounds that after the "coupling" step (b) there is no additional step of further size fractionating the conjugate preparation. (Office Action, page 2 at line 19 to page 3, line 4). Applicants point out that claim amendments discussed below have obviated these rejections and therefore, these rejections should be withdrawn.

Claims 44 and 69 have been amended to recite a step of further fractionation. Claim 44 has been amended to recite "subjecting the conjugate preparation to size fractionation." Claim 69 has been amended to recite "subjecting the epitope-coupled construct to size fractionation, thereby yielding a non-immunogenic epitope-coupled construct which is free of high molecular weight immunostimulatory molecules." Amendment of Claims 44 and 60 have obviated this rejection of Claims 44-69 and therefore, the rejection should be withdrawn.

Claim 58 is rejected for allegedly containing new matter on grounds that "about 20,000 daltons" is not recited in the original disclosure. Claim 58 has been cancelled, rendering the rejection moot with respect to this claim.

Claim 63 is rejected on grounds that "about 4 or 30" is not recited in the original disclosure. Claim 63 has been cancelled, rendering the rejection moot with respect to this claim.

Claim 64 is rejected on grounds that "about 6 to about 14" is not recited in the original disclosure. Claim 64 has been cancelled, rendering the rejection moot with respect to this claim.

Regarding Claim 65, the term "about" has been cancelled, rendering the rejection moot with respect to this claim.

Claim 67 has been amended to recite "wherein the non-immunogenic construct suppresses T-cell dependent antibody production." Support for this amendment is found on page 37 at lines 21-25 and on page 38 at lines 8-16. Amendment of Claim 67 has obviated this rejection and therefore the rejection should be withdrawn.

Claim rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 44-69 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, page 4 at lines 1-4).

Applicants point out that claim amendments discussed below have obviated these rejections and therefore, these rejections should be withdrawn.

In particular, step (b) of claims 44 and 69 is allegedly not enabled without the conducting of a post-coupling step to further size fractionate the conjugate preparation. (Office Action, page 4 at lines 4-5). As discussed above, Claims 44 and 69 have been amended to recite a step of further fractionation. Amendment of Claims 44 and 69 have obviated this rejection and therefore, the rejection should be withdrawn.

Claim 67 is rejected under 35 U.S.C. § 112, first paragraph, on grounds that the specification does not teach how to render the construct non-immunogenic construct "immunosuppressive to T-cells." (Office Action, page 4 at lines 12-16). Claim 67 has been amended to recite "wherein the non-immunogenic construct suppresses T-cell dependent antibody production" . Support for this amendment is found on page 37 at lines 21-25 and on page 38 at lines 8-16. Amendment of Claim 67 has obviated this rejection and therefore the rejection should be withdrawn.

Claim rejections under 35 U.S.C. § 102

Claims 44, 52-53, 56, 59-60, and 66-69 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Applicant's admitted state of the art at pages 6-10 of the present application. According to the Office Action, "other workers have coupled haptens to non-immunogenic soluble carriers that have a molecular weight appropriate for inducing tolerance, anergy, or immunosuppression." In particular, it is noted that Katz allegedly used poly (D-Glu, D-Lys) of molecular weight less than 100 kDa. Diener allegedly employed a CM-cellulose carrier of less than 100 kDa. (Office Action, page 5 at line 22 to page 6 at line 2). Applicants traverse this rejection for the reasons presented below.

To anticipate a claim, the reference must teach every element of the claim. "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.'" MPEP § 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The references cited on pages 6-10 of the present application do not disclose the claim limitations of Claim 44, which recites a method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, which copies bind to a B cell membrane immunoglobulin receptor specific for the

epitope but fail to form an immunon, comprising: (a) providing a non-immunogenic soluble carrier that has been subjected to a preparative sizing technique to remove substantially most high molecular weight non-immunogenic soluble carrier molecules, and an epitope molecule of a T-dependent antigen; (b) coupling two or more of the epitope molecules to the non-immunogenic soluble carrier that has been subjected to the preparative sizing technique of step (a) to yield a conjugate preparation; and (c) subjecting the conjugate preparation to size fractionation, thereby yielding a non-immunogenic construct which is free of high molecular weight immunostimulatory molecules.

Likewise, the references cited on pages 6-10 of the present application do not disclose the claim limitations of Claim 69, which recites a method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein construct-bound copies of the epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors, the method comprising: (a) providing a preparation of a non-immunogenic soluble carrier, wherein substantially all high molecular weight non-immunogenic soluble carrier molecules have been removed from the preparation, and an epitope of a T-dependent antigen; (b) coupling the two or more copies of the epitope to the non-immunogenic soluble carrier to yield a non-immunogenic epitope-coupled construct; and (c) subjecting the epitope-coupled construct to size fractionation, thereby yielding a non-immunogenic epitope-coupled construct which is free of high molecular weight immunostimulatory molecules. Because the references cited on pages 6-10 of the present application do not anticipate Claims 44, 52-53, 56, 59-60, and 66-69, the rejection under 35 U.S.C. § 102(b) should be withdrawn.

Claims 44-46, 49, 50-53, 59-61, and 63-69 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Barstad *et al.* (U.S. Patent No. 5,258,454). Applicants note that cancellation of Claims 53, 63 and 64 renders the rejection moot with respect to those claims. According to the Office Action, Barstad *et al.* allegedly disclose the induction of humoral anergy/unresponsiveness/tolerance/immunosuppression by administering conjugates of epitopic analogs coupled to a D-EK polymer carrier of 5,000-30,000 daltons. (Office Action, page 7 at lines. Applicants traverse this rejection for the reasons presented below.

To anticipate a claim, the reference must teach every element of the claim. "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.'" MPEP § 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In the present case, Barstad *et al.* disclose "conjugates of stable nonimmunogenic polymers and analogs of immunogens that possess the specific B cell binding ability of the immunogen but lack T cell epitopes . . ." (Barstad *et al.*, U.S. Patent No. 5,258,454, Abstract, emphasis added). Likewise, Barstad *et al.* describe their invention as "a composition for inducing specific B cell anergy to an immunogen comprising a conjugate of a nonimmunogenic biologically stable carrier polymer and an analog of the immunogen that (a) binds specifically to B cells to which the immunogen binds and (b) lacks the T-cell epitope(s) of the immunogen." (U.S. Patent No. 5,258,454, Col. 2 at line 65 to Col. 3 at line 3, emphasis added) Claim 1 of U.S. Patent No. 5,258,454 recites a method for making a conjugate useful for inducing specific B cell anergy to an immunogen, wherein "the conjugate lacks a T cell epitope." (U.S. Patent No. 5,258,454, Claim 1, Col. 11 at lines 27-28, emphasis added).

In contrast to the Barstad et al disclosure of an composition lacking T cell epitopes, independent Claims 44 and 69 of the present application both recite "[a] method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier . . . "(emphasis added). All claims that depend on Claim 44 likewise incorporate this recitation of an epitope of a T-dependent antigen. The Barstad *et al.* reference does not anticipate Claims 44-46, 49, 50-53, 59-61, and 63-69 because it does not disclose each and every element of these claims. Therefore, the rejection under 35 U.S.C. § 102(e) should be withdrawn.

Claims 44, 47, 50-53, 59-60, and 66-69 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Katz (U.S. Patent No. 4,191,668). According to the Office Action, the teachings of Katz allegedly correspond to the disclosure on page 6-10 of the present application, and the claims are rejected following the same rationale at that stated above. (Office Action, page 8 at lines 14-19).

As noted above, to anticipate a claim, the reference must teach every element of the claim. MPEP § 2131. Katz (U.S. Patent No. 4,191,668) does not disclose the claim limitations of Claim 44 or Claim 69 for the same reasons presented above, regarding the disclosure on page

6-10 of the present application. Claim 53 has been cancelled solely in the interest of advancing prosecution. Therefore, the Katz reference does not anticipate Claims 44, 47, 50-53, 59-60, and 66-69 and the rejection under 35 U.S.C. § 102(b) should be withdrawn.

CONCLUSION

For the reasons set forth herein, Applicants maintain that pending Claims 44-52, 54-57, 59-62, and 65-69 clearly and patentably define the invention, and respectfully request that a timely Notice of Allowance be issued in this case.

If the Examiner would like to discuss any of the issues raised in this Amendment, Applicant's representative can be reached at (858) 509-4093.

Applicants note that a Change of Address was filed on December 23, 2002. Applicants request that the Change of Address be entered into the record.

A Petition for Extension of Time under 37 C.F.R. § 1.136(a) and fee under 37 C.F.R. §1.17(a)(3) are being submitted herewith. If any additional fees are due, please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

Date: October 9, 2003

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